

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/70, A61F 13/20, G02C 7/02	A1	(11) International Publication Number: WO 95/07085 (43) International Publication Date: 16 March 1995 (16.03.95)
(21) International Application Number: PCT/US94/10175 (22) International Filing Date: 7 September 1994 (07.09.94) (30) Priority Data: 08/116,908 7 September 1993 (07.09.93) US (71) Applicant: ESCALON OPHTHALMICS, INC. [US/US]; 182 Tamarack Circle, Skillman, NJ 06558 (US). (72) Inventor: BENEDETTO, Dominick, A.; 124 Avenue B, Bayonne, NJ 07002 (US). (74) Agent: SAUNDERS, Thomas, M.; Lorusso & Loud, 440 Commercial Street, Boston, MA 02109 (US).		(81) Designated States: CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE		
(57) Abstract		
<p>This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grad viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm²; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

1 SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

2

3

4

5

6

7

8

Field of the Invention.

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

18

50

...

21

22

23

24

25

26

27

28

1 of viscoelastic properties as related to the surface activity,
2 or the solution fracturing under applied stress. In particular,
3 it is surprising to manipulate or enhance the physical
4 properties of viscoelastic solutions of mucopolysaccharides,
5 hyaluronic acid, and/or chondroitin sulfate. It is believed
6 that disclosure here of a processes to provide hyaluronic acid
7 and species thereof with controlled surface activity is unique.
8 This is also especially true of the control of surface activity
9 of mucopolysaccharide solutions by the addition of biologically
10 compatible surfactants. A characteristic feature of
11 biologically compatible surfactants is the absence of observed
12 alteration in cellular physiology upon contact. Early work in
13 the viscoelastic field was presented by the inventor of this
14 disclosure and his associates. Benedetto, D.A. et. al.,
15 Viscoelastic Materials: Basic Science and Clinical Application,
16 (Symposium Proceedings), University of Manchester, England, July
17 17-19, 1986.

18
19 As to commercial production, a review of the ophthalmic
20 pharmacopoeia reveals there are several viscoelastic solutions
21 produced for ocular and intraocular use during ophthalmic
22 surgery. The most common application for these solutions is in
23 the intraocular lens implant procedure for human cataract
24 surgery. This procedure involves extraction of the cataractous
25 human lens through a small surgical opening in the eye and the
26 replacement of the lens by a prosthetic intraocular lens placed
27 in situ. Biocompatible polymers presently or previously in use
28 are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

1 a combined solution of hyaluronic acid and chondroitin sulfate
2 (Viscoat™); and a hydroxypropylmethylcellulose solution
3 (Occucoat™). Research conducted recently demonstrates that
4 Healon™ and Amvisc™ are not surface active, but Viscoat™ and
5 Occucoat™ are.

6 Chondroitin sulfate does not exist as a free polysaccharide
7 in its native state, but as a proteoglycan. It is obtained from
8 sources associated with protein contaminants. The avoidance of
9 chondroitin sulfate avoids a potential source of pyrogenic
10 reaction, and the substantial cost associated with protein
11 removal.

12 Summary of the Invention

13 The invention presented herein discloses modified
14 mucopolysaccharide or viscoelastic solutions for use as
15 biologically active therapeutic infusions. In one form of the
16 invention, the mucopolysaccharide solution is formed from a
17 viscoelastic fraction and a buffer fraction. It has been found
18 that when a new synthetic molecule acyl-substituted hyaluronic
19 acid is employed as the viscoelastic fraction, control of
20 surface activity is achieved. An indicia of this is the
21 decrease of the surface tension of the solution which is now
22 within predetermined limits discussed below. Surface tension
23 modification is also accomplished with viscoelastic fractions in
24 which the acyl-substituted hyaluronic acid is mixed with one or
25 more of hyaluronic acid; and hydroxypropylmethylcellulose. In
26 certain applications, the viscoelastic solution of this
27 invention is used in a method of adhering a contact lens to the
28

1 surface of the eye, such as in association with procedures
2 permitting a medical professional to view ocular and intraocular
3 structures through the contact lens and through the viscoelastic
4 solution. This is particularly useful in facilitating surgical
5 procedures. In another application, the viscoelastic solution of
6 this invention is used by injection the solution into or under
7 structures or tissues within the eye, such as to dissect tissue
8 off of the retina.

9
10 In the broadest terms, surface active viscoelastic
11 solutions with controlled solution properties, are characterized
12 by surface tension, equilibrium contact angle, dynamic
13 viscosity, and cohesiveness (the measure of solution fracture
14 under stress). In a particular embodiment, this invention is
15 delimited by the three dimensional representation of Fig. 7.

16 In one example, bioengineered hyaluronic acid from a
17 bacterial source with an average molecular weight of 50,000 is
18 modified by acyl substitution with three to twenty carbon atom
19 acyl groups so that the resultant surface tension of such a
20 solution is between 40 and 65 dynes/cm². In the practice of
21 this invention, a viscoelastic solution having a surface tension
22 of less than about 56 dynes/cm², and more particularly, less
23 than about 50 dynes/cm² is of particular advantage.

24
25 This invention comprises a modified mucopolysaccharide
26 solution for use as a biologically active therapeutic infusion
27 comprising:
28

1 a pharmaceutical grade viscoelastic fraction selected from
2 the group consisting of acyl-substituted hyaluronic acid having
3 acyl groups thereof with three to twenty carbon atoms,
4 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
5 thereof, and absent chondroitin sulfate said fraction having a
6 surface tension of between 40 and 65 dynes/cm²; and,

7 optionally with a physiological buffer fraction, such that
8 the viscoelastic comprises about a 0.1% percent of the solution
9 to about 5% of the solution, by weight, and preferably from
10 about 0.5 % to about 3%;

11 said modified mucopolysaccharide solution having a
12 viscosity of between 10,000 and 100,000 centipoise when measured
13 at a shear rate of 3 sec⁻¹ at 25°C; and,

14 optionally wherein the modified mucopolysaccharide
15 solution has a surface tension of less than about 56 dynes/cm²,
16 and further a surface tension of less than about 50 dynes/cm²;
17 and further,

18 optionally wherein the solution has an osmolality of from
19 about 250 to about 400 milliosmoles, or is generally isotonic
20 with ophthalmic tissue.

21 In some embodiments the modified mucopolysaccharide
22 solution viscoelastic fraction has an average molecular weight
23 of at least 50,000. Reference is further made to the
24 viscoelastic fraction being an acyl-substitute hyaluronic acid
25 having acyl groups thereof with three to twenty carbon atoms.

26 In particular applications the modified mucopolysaccharide
27 solution of this invention includes a surfactant fraction of a
28 biocompatible component selected from a group consisting of

1 phospholipids, monoglycerides, free fatty acids, free fatty acid
2 soaps, cholesterol, fluorocarbons, silicones, and nonionic
3 surfactants, with the surfactant present in an amount sufficient
4 to produce the required surface tension. In particular, a
5 biological surfactant fraction of a free fatty acid is present
6 in an amount of less than 1 mg/ml. Further embodiments include
7 a surfactant fraction of a biocompatible component selected from
8 a group consisting of phospholipids, monoglycerides, free fatty
9 acids, free fatty acid soaps, cholesterol, fluorocarbons,
10 silicones, and nonionic surfactants, said surfactant present in
11 an amount less than 10 micrograms/ml. In a preferred embodiment
12 the surfactant fraction of biocompatible component is a free
13 fatty acid.

14 In a further embodiment the modified mucopolysaccharide
15 solution has a viscoelastic fraction of a mixture of
16 acyl-substituted hyaluronic acid and hyaluronic acid, and
17 particularly with a surfactant fraction of a biocompatible
18 component selected from a group consisting of phospholipids,
19 monoglycerides, free fatty acids, free fatty acid soaps,
20 cholesterol, fluorocarbons, silicones, and nonionic surfactants,
21 with surfactant present in an amount sufficient to produce the
22 required surface tension, usefully in an amount less than
23 10 micrograms/ml. Preferred surfactants are free fatty acids
24 such as oleic acid.

25 Particular modified mucopolysaccharide solutions of the
26 invention are characterized by aspiration through a 0.3 mm
27 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and
28 particularly in a range of 50 to 200 mm Hg, wherein the solution

1 is easily fractured. Similarly, those solutions with an
2 aspiration profile of from about horizontal up to about 1.5 and
3 more particularly from about horizontal to about 1.0 are
4 preferred.

5 In another embodiment this present invention comprises a
6 modified mucopolysaccharide solution for use during ophthalmic
7 surgery for protection of the internal ocular structures
8 including corneal endothelium from accidental touch by surgical
9 instruments, yet permitting of observation of said structures
10 comprising:

11 an optically clear polymeric fraction of high purity
12 mucopolysaccharides selected from the group consisting of
13 acyl-substituted hyaluronic acid having acyl groups thereof with
14 three to twenty carbon atoms, hyaluronic acid,
15 hydroxypropylmethylcellulose and mixtures thereof and absent
16 chondroitin sulfate, said fraction having a surface tension of
17 between 40 and 65 dynes/cm²; and,

18 optionally a physiological buffer fraction, such that the
19 viscoelastic comprises about a 0.1% percent of the solution to
20 about 5% of the solution, by weight, and preferably from about
21 0.5 % to about 3%;

22 said modified mucopolysaccharide solution having a
23 viscosity of between 10,000 and 100,000 centipoise when measured
24 at a shear rate of 3 sec⁻¹ at 25 C; and,

25 wherein said mucopolysaccharide fraction has an average
26 molecular weight of at least 50,000; and,
27
28

1 a biological surfactant fraction of a free fatty acid
2 present in an amount less than 10 micrograms/ml; and,
3 optionally wherein the modified mucopolysaccharide
4 solution has a surface tension of less than about 56 dynes/cm²,
5 and further a surface tension of less than about 50 dynes/cm².

6 In some embodiment of this modified mucopolysaccharide
7 solution a particular polymeric fraction is hyaluronic acid.

8 Particular modified mucopolysaccharide solutions of the
9 invention are characterized by aspiration through a 0.3 mm
10 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and
11 particularly in a range of 50 to 200 mm Hg, wherein the solution
12 is easily fractured, which optionally include those solutions
13 with an aspiration profile of from about horizontal up to about
14 1.5 and more particularly from about horizontal to about 1.0.

15 Another embodiment of the present invention includes a
16 pharmaceutically acceptable modified mucopolysaccharide solution
17 (particularly a surface active mucopolysaccharide) absent
18 chondroitin sulfate having a surface tension of between 40 and
19 65 dynes/cm²; and,

20 a viscosity of between 10,000 and 100,000 centipoise
21 (particularly an average molecular weight of at least 50,000)
22 when measured at a shear rate of 3 sec⁻¹ at 25 C.

23 optionally wherein the modified mucopolysaccharide
24 solution has a surface tension of less than about 56 dynes/cm²,
25 and further a surface tension of less than about 50 dynes/cm².

26 In this embodiment of a modified mucopolysaccharide
27 solution a particular polymeric fraction is hyaluronic acid.
28

1 In certain applications the mucopolysaccharide solution
2 further comprises a biological surfactant selected from a group
3 consisting of phospholipids, monoglycerides, free fatty acids,
4 free fatty acid soaps, cholesterol, fluorocarbons, silicones,
5 and nonionic surfactants.

6 Yet a further embodiment of the invention includes a method
7 of protecting internal ocular structures during ocular surgery
8 and retarding aspiration of material from the ocular surgery
9 site by the steps of:

10 intraocularly introducing biologically active therapeutic
11 infusion amount of a modified mucopolysaccharide solution
12 comprising:

13 a pharmaceutical grade viscoelastic fraction selected from
14 the group consisting of acyl-substituted hyaluronic acid having
15 acyl groups thereof with three to twenty carbon atoms,
16 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
17 thereof and absent chondroitin sulfate, said fraction with a
18 surface tension of between 40 and 65 dynes/cm² (particularly
19 less than about 56 and more particularly less than about 50
20 dynes/cm²); and,

21 optionally a physiological buffer fraction, such that the
22 viscoelastic comprises about a 0.1% percent of the solution to
23 about 5% of the solution, by weight, and preferably from about
24 0.5 % to about 3%;

25 said modified mucopolysaccharide solution having a
26 viscosity of between 10,000 and 100,000 centipoise when measured
27 at a shear rate of 3 sec⁻¹ at 25 C. In such embodiment a
28

1 preferred method entails intraocularly introducing biologically
2 active therapeutic infusion amount of a modified
3 mucopolysaccharide solution by a syringe of about 1.13 cm^2 in
4 cross section or less, and optionally about 0.57 cm^2 or less,
5 and further optionally about 0.16 cm^2 . In certain embodiments a
6 "sloped" syringe absent sharp reductions in cross sectional area
7 is useful.

8 Further in this method the invention includes particular
9 modified mucopolysaccharide solutions characterized by
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to
12 200 mm Hg, wherein the solution is easily fractured. Similarly,
13 those solutions with an aspiration profile of from about
14 horizontal up to about 1.5 and more particularly from about
15 horizontal to about 1.0 are preferred.

16 An additional embodiment of the invention includes a method
17 of protecting internal ocular structures during ocular surgery
18 by providing a viscoelastic solution that coats ocular
19 structures at a surgical site such that aspiration of the
20 viscoelastic solution is retarded, said method being:

21 intraocularly introducing biologically active therapeutic
22 infusion amount of a modified mucopolysaccharide solution absent
23 chondroitin sulfate and having a surface tension of between 40
24 and 65 dynes/cm^2 (particularly less than about 56 and more
25 particularly less than about 50 dynes/cm^2); and,
26

27
28

1 a viscosity of between 10,000 and 100,000 centipoise when
2 measured at a shear rate of 3 sec^{-1} at 25 C. In such embodiment
3 a preferred method entails intraocularly introducing
4 biologically active therapeutic infusion amount of a modified
5 mucopolysaccharide solution by a syringe of about 1.13 cm^2 in
6 cross section or less, and optionally about 0.57 cm^2 or less,
7 and further optionally about 0.16 cm^2 .

8 Further in this method the invention includes particular
9 modified mucopolysaccharide solutions characterized by
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to
12 200 mm Hg, wherein the solution is easily fractured. Similarly,
13 those solutions with an aspiration profile of from about
14 horizontal up to about 1.5 and more particularly from about
15 horizontal to about 1.0 are preferred.

16 A next method of the present invention includes a method of
17 protection of internal ocular structures including corneal
18 endothelium from accidental touch by surgical instruments, yet
19 permitting of observation of said structures comprising:

20 intraocularly introducing a modified mucopolysaccharide
21 solution during ophthalmic surgery wherein said solution
22 comprises

23 an optically clear polymeric fraction of high purity
24 mucopolysaccharides selected from the group consisting of
25 acyl-substituted hyaluronic acid having acyl groups thereof with
26 three to twenty carbon atoms, hyaluronic acid,
27 hydroxypropylmethylcellulose and mixtures thereof and absent
28

1 chondroitin sulfate, said fraction having a surface tension of
2 between 40 and 65 dynes/cm² (particularly less than about 56 and
3 more particularly less than about 50 dynes/cm²); and,

4 optionally a physiological buffer fraction, such that the
5 viscoelastic comprises about a 0.1% percent of the solution to
6 about 5% of the solution, by weight, and preferably from about
7 0.5 % to about 3%;

8 said modified mucopolysaccharide solution having a
9 viscosity of between 10,000 and 100,000 centipoise when measured
10 at a shear rate of 3 sec⁻¹ at 25 C; and,

11 wherein said mucopolysaccharide fraction has an average
12 molecular weight of at least 50,000; and,

13 a biological surfactant fraction of a free fatty acid
14 present in an amount less than 10 micrograms/ml.

15 In such embodiment a specific method entails intraocularly
16 introducing biologically active therapeutic infusion amount of a
17 modified mucopolysaccharide solution by a syringe of about 1.13
18 cm² in cross section or less, and optionally about 0.57 cm² or
19 less, and further optionally about 0.16 cm².

20 Further in this method the invention includes particular
21 modified mucopolysaccharide solutions characterized by
22 aspiration through a 0.3 mm cannula at a vacuum pressure in a
23 range of 5 to 400 mm Hg, and particularly in a range of 50 to
24 200 mm Hg, wherein the solution is easily fractured. Similarly,
25 those solutions with an aspiration profile of from about
26 horizontal up to about 1.5 and more particularly from about
27 horizontal to about 1.0 are preferred.

28

1 A next embodiment of the invention comprises a modified
2 mucopolysaccharide solution for use as a biologically active
3 therapeutic infusion comprising:

4 a pharmaceutical grade viscoelastic fraction selected from
5 the group consisting of acyl-substituted hyaluronic acid having
6 acyl groups thereof with three to twenty carbon atoms,
7 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
8 thereof, and absent chondroitin sulfate said fraction having a
9 surface tension of between 40 and 65 dynes/cm² (particularly
10 less than about 56 and more particularly less than about 50
11 dynes/cm²); and,

12 said modified mucopolysaccharide solution having a
13 viscosity of between 10,000 and 100,000 centipoise when measured
14 at a shear rate of 3 sec⁻¹ at 25°C.

15 This invention encompasses a modified mucopolysaccharide
16 solution for use as a biologically active therapeutic infusion
17 comprising:

18 a pharmaceutical grade viscoelastic fraction selected from
19 a group consisting of an acyl-substituted hyaluronic acid having
20 acyl groups thereof with three to twenty carbon atoms and
21 mixtures of said acyl-substituted hyaluronic acid with
22 hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B,
23 chondroitin sulfate C, and hydroxypropylmethylcellulose, said
24 fraction with a surface tension of between 40 and 65 dynes/cm²;
25 particularly a viscoelastic fraction has an average molecular
26 weight of at least 50,000; and,
27
28

1 optionally a physiological buffer fraction, such that the
2 viscoelastic comprises about a 0.1% percent of the solution to
3 about 5% of the solution, by weight, and preferably from about
4 0.5 % to about 3%;

5 whereby, upon infusion of modified mucopolysaccharide
6 solution at the site, the surface activity of the solution
7 enhances coating of the site.

8 A specific modified mucopolysaccharide solution is one with
9 an acyl-substituted hyaluronic acid, and a preferred viscosity
10 is between 10,000 and 100,000 centipoise when measured at a
11 shear rate of 3 sec^{-1} at 25°C , and optionally further including
12 a surfactant fraction of a biocompatible component selected from
13 a group consisting of phospholipids, monoglycerides, free fatty
14 acids, free fatty acid soaps, cholesterol, fluorocarbons,
15 silicones, and nonionic surfactants, said surfactant present in
16 a trace amount sufficient to produce said surface tension. In
17 one embodiment the surfactant is present in an amount less than
18 10 micrograms/ml. A preferred surfactant is oleic acid. A
19 preferred modified mucopolysaccharide solution comprises a
20 mixture of an acyl-substituted hyaluronic acid and hyaluronic
21 acid.

22 In a particular application this invention includes a
23 modified mucopolysaccharide solution for use a biologically
24 compatible therapeutic infusion comprising:

25 a pharmaceutical grade viscoelastic fraction selected from
26 a group consisting of hyaluronic acid, chondroitin sulfate A,
27 chondroitin sulfate B, and chondroitin sulfate C, said fraction
28 having an average molecular weight of at least 50,000.

1 a surfactant fraction of a biocompatible component selected
2 from a group consisting of phospholipids, monoglycerides, free
3 fatty acids, free fatty acid soaps, cholesterol, fluorocarbons,
4 silicones, and nonionic surfactants, said surfactant present in
5 a trace amount sufficient to produce a surface tension of
6 between 40 and 65 dynes/cm²; and,

7 optionally a physiological buffer fraction, such that the
8 viscoelastic comprises about a 0.1% percent of the solution to
9 about 5% of the solution, by weight, and preferably from about
10 0.5 % to about 3%;

11 whereby, upon infusion of modified mucopolysaccharide
12 solution at the site, the surface activity of the solution
13 enhances coating of the site and results in retardation of
14 aspiration at the site. A preferred modified mucopolysaccharide
15 solution has a viscoelastic fraction of hyaluronic acid, and,
16 optionally, a viscosity of between 10,000 and 100,000 centipoise
17 when measured at a shear rate of 3 sec⁻¹, and further
18 optionally, a surfactant, particularly oleic acid, and
19 particularly with surfactant present in an amount less than 10
20 micrograms/ml.

21 In one embodiment this invention includes a modified
22 mucopolysaccharide solution for use during ophthalmic surgery
23 for protection of the internal ocular structures comprising:

24 an optically clear polymeric fraction of high-purity
25 mucopolysaccharides and mixtures thereof, said polymeric
26 fraction selected from the group consisting of hyaluronic acid,
27 chondroitin sulfate A, chondroitin sulfate B, chondroitin

28

1 sulfate C, and mixtures of hyaluronic acid, chondroitin sulfate
2 A, chondroitin sulfate B and chondroitin sulfate C with an
3 average molecular weight of at least 50,000;

4 a biological surfactant fraction of a free fatty acid
5 present in an amount of less than 1 mg/ml; and,

6 optionally a physiological buffer fraction, such that the
7 viscoelastic comprises about a 0.1% percent of the solution to
8 about 5% of the solution, by weight, and preferably from about
9 0.5 % to about 3%;

10 whereby, upon the modified mucopolysaccharide solution
11 being placed in the eye space during surgery, the surgeon can
12 observe the ocular and intraocular structure through the
13 optically clear solution, and the corneal endothelium is
14 protected from accidental touch by surgical instruments, ocular
15 and intraocular prosthetic devices, and in ocular and
16 intraocular irrigating solutions, particularly wherein the
17 polymeric fraction is hyaluronic acid, and particularly wherein
18 the solution has a viscosity of between 10,000 and 100,000
19 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C .

20 An additional embodiment of this invention is a method of
21 adhering a contact lens to the surface of the eye in
22 operational-optical connection with said eye, by the step of
23 interposing between said lens and said eye surface an adhering
24 amount of substantially transparent modified mucopolysaccharide
25 solution of this invention. In the practice of this method, an
26 apparatus comprising a contact lens and a layer of transparent
27 modified mucopolysaccharide solution is employed. Preferably
28 the optical properties of such lens/solution unit will be

1 configured to facilitate observation of internal ophthalmic
2 structures when the observer is positioned to peer directly
3 through the lens. Alternatively, the "observer" may be a
4 television, film or other camera directed into the lens.
5 Further, the camera lens may substitute for the contact lens,
6 and thus with a layer of the mucopolysaccharide solution of this
7 invention, be in direct contact with the eye.

8 A yet further embodiment of this invention is a method of
9 hydraulically positioning intra-optic structures or tissues by
10 the step of applying against such tissues under elevated
11 hydrostatic pressure the modified mucopolysaccharide solution of
12 this invention. Typically this would be applied to dissect or
13 elevate hyperplastic tissue that grows over the retina in
14 certain pathologies. The degree of elevation of hydrostatic
15 pressure would be that sufficient to move the intended tissue.

16 An additional aspect of this invention is based upon
17 ophthalmic osmolality. Osmolality of from about 250
18 milliosmoles to about 400 milliosmoles is essentially isotonic
19 to optic structures. Lower osmolality will cause optic
20 structures to swell and higher osmolality will cause shrinkage.

21

22

23

24

25

26

27

28

1
2 **Brief Description of the Drawings**

3 Fig. 1 is a plot of Kc/R_g against concentration, C. The
4 material tested is high molecular weight HA. The molecular
5 weight was obtained from the inverse of the abscissa
6 extrapolated to zero concentration.

7 Fig. 2 is a plot of maximum load versus time for high
8 molecular weight HA. The maximum load was determined as the
9 largest load needed to force a sample of viscoelastic from a
10 syringe through a 23 gauge needle.

11 Fig. 3. is a graphic comparison of the surface tension of
12 one embodiment of of a solution of the present invention as
13 compared to the surface tension of a commercially available HPMC
14 ocular solution, and a commercially available HA ocular
15 solution.
16

17 Fig. 4 is a graphic comparison of the viscosity of one
18 embodiment of a solution of the present invention as compared
19 with other, commercially available, ocular solutions, and
20 measured at a shear rate of 0.35 sec^{-1} . Standard deviation is
21 shown in gray, and the average values in black. All columns
22 except E and F are statistically different than B, Healon™

23 Fig. 5 is a plot comparison of the aspiration
24 characteristics of the *in situ* retention of solutions embodying
25 the present invention as compared other viscoelastic ocular
26 solutions.
27

28 Fig. 5(a) repeats Fig. 5 with a preferred range shaded.

1 Fig. 6 is a plot of viscosity against surface tension
2 enclosing a preferred range for solutions of the present
3 invention.
4

5 Fig. 7 is a three dimensional plot of viscosity against
6 surface tension against "aspiration profile" (the slope of the %
7 of aspiration between 50 mmHg and 90 mmHg under test conditions
8 as plotted in Fig. 5, and excluding sigmoidal curves) enclosing
9 in cubic representation a of viscoelastic solutions of the
10 present invention.

11 Fig. 8 is a graphic representation of stress (MPa) recorded
12 by injecting various solutions of varying viscosity from a
13 syringe and through a 23 gauge needle.
14

15 Fig. 9(a), (b), and (c) represent various embodiments of
16 "sloped" syringe absent sharp reductions in cross sectional
17 area.

18 Fig. 10(a) and (b) are diagrammatic representations of
19 various embodiments of an apparatus for viewing the interior of
20 the eye (depicted in contact with an eye).
21

22 Detailed Description of the Invention

23 In general terms, viscoelastic solutions are placed in the
24 anterior chamber of the eye during ocular and intraocular lens
25 implant surgery, replacing the fluid aqueous humor of the eye.
26 Clearly, hosts suitable for application of the present materials
27 and methods are ocular and intraocular site of animal requiring
28

1 such material. In particular, host sites are mammalian eyes,
2 particularly those of humans, and most particularly the anterior
3 chamber thereof. By nature of their viscosity (10,000 to 1
4 million times greater than that of aqueous humor), viscoelastic
5 solutions allow the eye to maintain its normal shape and ocular
6 and intraocular structural relationships during cataract
7 extraction and lens implantation. When the fluid aqueous humor
8 leaks from the eye, as when the eye is opened by incision at the
9 time of surgery, the anterior structures of the eye collapse.

10 There is no space within the anterior segment of the eye within
11 which the surgeon can place instruments for cataract extraction
12 without damaging ocular and intraocular structures by touch from
13 his instruments. Air may be used to maintain this space, but it
14 is more likely to leak from the eye compared to a viscous
15 solution. In addition, air on top of other ocular fluids, does
16 not allow the surgeon to visualize ocular and intraocular
17 structures, as effectively as through clear viscoelastic
18 solution. Viscoelastic solutions are fluids which resist flow
19 by nature of their high viscosity. These fluids are elastic
20 because they have a "memory." They return to approximately
21 their original shape after stretch. These solutions are
22 optically clear and are basically aqueous solutions of higher
23 molecular weight polymers in the molecular weight range of
24 50,000 to 8 million.

25 As used herein, in reference to HPMC, the term "low" in
26 reference to "low molecular weight" HPMC, "HPMC(L)," shall mean
27 below about 250,000 MW and particularly below about 150,000 MW,
28 while "high" molecular weight HPMC, "HPMC(H)," shall mean above

1 about 250,000 MW and particularly above about 300,000 MW. In
2 reference to HA, the term "low" in reference to "low molecular
3 weight" HA, "HA(L)," shall mean below about 1,500,000 MW, and
4 particularly below about 700,000 MW, while "high" molecular
5 weight HA, "HA(H)," shall mean above about 1,500,000 MW, and in
6 particular above about 3,000,000 MW, and more particularly above
7 about 5,000,000 MW.

8 In addition to being viscous and elastic, a mild degree of
9 surface activity is a desirable property of viscoelastic
10 solutions. Surface activity is a measure of the ability of a
11 solution to coat or spread on a surface. Solutions which coat
12 the internal structures of the eye are better able to protect
13 the eye from accidental touch by surgical instruments or an
14 intraocular lens. In addition, these solutions protect the eye
15 from irrigation damage by irrigating solutions used in routine
16 cataract surgery. Viscoelastic solutions which are not surface
17 active and do not fracture at aspiration pressures used during
18 cataract surgery are too easily aspirated from the eye during
19 cataract surgery. The surgeon is then faced with lack of
20 protective ophthalmic solution, which necessitates replacement
21 of viscoelastic at additional cost.
22

23 Particular note is made of the distinction between
24 viscosity and pseudoplasticity (which includes thixotropy).
25 Viscosity is the propensity of a solution to resist flow.
26 Pseudoplasticity is the general case of a change in viscosity
27
28

1 with applied force, which may or may not be reversible.
2 Thixotropy describes reversible shear thinning, limited largely
3 to the period while subject to shear.

4
5 Surface tension is a measure of the tendency of molecules
6 within a solution to attract or repel each other. With high
7 mutual attraction, the solution has a high surface tension and
8 the solution is cohesive. Without being bound by any particular
9 theory, it is believed that at a solution interface (air/liquid,
10 liquid/liquid, liquid/solid)) of a solution of high surface
11 tension, the tendency would be for solution molecules to be
12 drawn back into the solution. In a solution of low surface
13 tension (i.e., a surfactant type solution) solution molecules
14 accumulate at an interface because the molecules are not
15 completely soluble within the bulk solution. It is presumed
16 that the hydrophobic/hydrophilic structure of surfactant
17 molecules cause them to accumulate at a solution interface,
18 representing the lowest energy state.

19 Particular attention is drawn to the unique confluence of
20 physical characteristics present in the viscoelastic solution of
21 the present invention. Considering viscosity, Fig. 4 discloses
22 that a variety of viscosities (Fig. 4, Examples E-H) may be
23 obtained within the practice of this invention, while still
24 presenting the required surface tension and aspiration profile.
25 Viscosity is presented in m Pa·s or millipascal·seconds. One
26 Pa·s equals 1000 centipoise, and one mPa·s equals 1 centipoise.
27 Fig 4. data was obtained at a shear rate of 0.35 sec^{-1} . The
28 solutions represented are as follows: A is 2% HPMC(L) and a

1 molecular weight of about 200,000 with a viscosity of 98 cps; B
2 is 2% HPMC with a viscosity of 3680 cps; C is 1% HA(L) (L
3 denotes an average MW of about 0.8×10^6) solution with a
4 viscosity of 424 cps; D is 1% HA(H) (H denotes an average MW of
5 about 2.1×10^6) solution with a viscosity of 21,845 cps; E is a
6 mixture of 2% HPMC(L) and 1% HA(L) with a viscosity of 2,095
7 cps; F is a mixture of 2% HPMC(L) and 1% HA(H) with a viscosity
8 of 38,460 cps; G is a mixture of 2% HPMC(H) and 1% HA(L) with a
9 viscosity of 25,344 cps; and H is a mixture of 2% HPMC(H) and 1%
10 HA(H) with a viscosity of 56,691 cps. The substantial and
11 synergistic increase in HPMC viscosity in combination with a
12 viscoelastic, such as, HA is noted.

13
14 Fig. 3 compares the surface tension of various ocular
15 solutions. Solution A is Occucoat™, a commercially available
16 HPMC solution, measured at 1:10 dilution as having a surface
17 tension of 43.0 ± 1.41 dynes/cm; Solution B is Healon™, a
18 commercially available HA solution, measured at 62.7 ± 6.51
19 dynes/cm, Solution C, low molecular weight HPMC, and Solution D,
20 high molecular weight HPMC were measured at about $50 \pm .75$
21 dynes/cm; Solution E, low molecular weight HA, and Solution F,
22 high molecular weight HA were measured at about 70 ± 2.25
23 dynes/cm; Solutions G through J are mixtures of 1% HA and 2%
24 HPMC all having a surface tension of about 50 ± 0.58 dynes/cm .
25 Specifically Solution G is HA(L) and HPMC(L). Solution H is
26 HA(H) and HPMC(L). Solution I is HA(L) and HPMC(H). Solution J

1 is HA(H) and HPMC(H). Note that Fig. 3 solutions A, C, D, G-J
2 exhibit surface tension statistically significantly different
3 than B, Healon™.

4 Further note is made of the fracture and aspiration
5 characteristics of the mucopolysaccharide solutions of this
6 invention. In ocular surgery, a tiny cannula is used to
7 inject/remove viscoelastic solutions. The claimed solutions
8 easily fracture when vacuum is applied by a cannula. Thus to
9 remove all of such solution, the cannula must be repeatedly
10 moved to remain in contact with the solution. In contrast, a
11 typical solution of high molecular weight as known in the prior
12 art fall into two groupings. One, typified by Healon™, an HA
13 solution will not fracture easily, nor will it elute in
14 solutions typically present during ophthalmic surgery and
15 generally aspirates only in a bolus. The other grouping
16 comprises solutions "incohesive" solutions. "Incohesive"
17 solutions elute so rapidly that, they are removed from the
18 ocular surgical site by irrigation fluids. This rapid elution
19 destroys the viscosity, coating and shock absorbing properties
20 for which they were being used, leaving the field unprotected.

21 A useful measure of fracture and aspiration characteristics
22 of various solutions is set forth in Fig. 5. In particular,
23 Fig. 5 is a clear representation of the achievement of
24 protective *in situ* retention of a solution embodying the present
25 invention as compared to an HA ocular solution -- independent of
26 viscosity. The aspiration behavior of HA is seen to be
27 generally sigmoidal. At low vacuum, only small amounts of HA
28

1 are aspirated, while at vacuums of about 40 mm Hg, almost 100%
2 of the HA is removed. In contrast, a mixture of HA and HPMC, is
3 removed in a manner generally linear to the amount of vacuum
4 applied, permitting gradual removal, which may be continued to
5 almost total removal, but not removal generally as a single
6 bolus. Again, this linear removal profile may be obtained with
7 solutions of a viscosity similar to that of HA alone, and
8 substantially above the viscosity of HPMC alone. Particularly
9 useful viscoelastic solutions are those whose aspiration
10 characteristics are non-sigmoidal under the described
11 experimental conditions, and most particularly those which are
12 generally linear with a slope of between about horizontal and
13 about 1.5, (and preferably between about horizontal and about 1)
14 as presented in Fig. 5 as percentage aspiration against mmHG
15 from about 50 mm HG to about 90 mm HG, using a 23 gauge needle.
16 The procedure is more fully described in Aspiration Profile
17 (below). A preferred range is shaded in Fig. 5(a) which
18 reproduces Fig 5.

19 Figs. 6 and 7 define meets and bounds of particular
20 embodiments of this invention. Fig. 6 is seen to delimit
21 suitable viscoelastics by viscosity and surface tension.
22 Particularly preferred are those solutions of less than 56
23 dynes/cm and more particularly, those of less than 50 dynes/cm
24 surface tension. Occucoat™ is plotted as point "I" and Healon™
25 is plotted as point "II." Fig. 7 graphically distinguishes the
26 chondroitin free viscoelastic solution of the present invention
27 from particular commercial viscoelastic solutions. Three
28

1 parameters, viscosity, surface tension, and aspiration profile
2 are presented. It is the three dimensional area circumscribed
3 by these parameters that are particularly useful. More
4 particularly is the circumscribed area, below 56 dynes/cm in
5 surface tension and more particularly still, the circumscribed
6 area below 50 dynes/cm surface tension.

7
8 Given the delimiting parameters of the claimed viscoelastic
9 solutions, a general protocol to achieve such solutions is
10 presented. Viscosity is increased or decreased in relation to
11 highest molecular weight viscoelastic material or polymeric
12 material present. If the viscosity of that highest molecular
13 weight material is the viscosity desired, no adjustment is
14 required. If lower viscosity is desired, increased dilution, or
15 substitution of material of identical structure, but lower
16 molecular weight, decreases viscosity. When increasing
17 dilution, attention must be paid to the resulting solution
18 osmolarity. Aspiration characteristics of the invention are
19 modified by admixing viscoelastic polymers with low molecular
20 weight polymers of the same or other species, including
21 polysaccharides such as HPMC. Such additions increase ease of
22 fracture on aspiration. Surface tension is reduced by addition
23 of surfactant or by modification of a non-surface active
24 molecule to be surface active. Particular note is made of the
25 surface activity of HPMC. In the case of HA, surface activity
26 adjustment entails addition of a lipophilic acyl side chain or
27 chains. Osmolality is adjusted by modification of the
28 solute/solvent ratio.

1 All of the foregoing parameters are most easily adjusted by
2 empirical methods such as a checkerboard type assay, increasing
3 the amount of each particular factor (serial dilution) until the
4 desired characteristic is obtained. However, approximate
5 methods of calculation are possible.

6 By this disclosure, non-surface active viscoelastic
7 solutions are modified to make them surface active. This can be
8 accomplished by the addition of any one of many biocompatible
9 surfactants, or by substitution or admixture of hyaluronic acid
10 polymer in a viscoelastic solution with hyaluronic acid polymer
11 having a lipophilic side chain. A lipophilic acyl side chain
12 substituted hyaluronic acid renders the previously completely
13 water soluble molecule surface active. Biological surfactants
14 belong to the following categories of chemical substances:
15 phospholipids, monoglycerides, free fatty acids or fatty acid
16 soaps, cholesterol, and pharmaceutical grade nonionic
17 surfactants. Though it is understood that HPMC has some
18 surfactant activity, as used herein, biological surfactants
19 excludes HPMC. Preliminary results with oleic acid, a fatty
20 acid component of phospholipids which composes most mammalian
21 cell membranes, indicate that at a concentration of 1 microgram
22 oleic acid per ml of solution can provide moderate surface
23 activity to a solution which was not previously surface active.
24 During routine cataract surgery, particular claimed viscoelastic
25 solutions with surface activity will coat ocular, and
26 intraocular structures, and a prosthetic lens during its
27 placement into the eye.
28

1 In the present invention, a modified mucopolysaccharide
2 solution is disclosed. The modified mucopolysaccharide solution
3 is used as a biologically active therapeutic infusion, most
4 typically during ophthalmic surgery, such as one ocular and
5 intraocular lens implant procedure. In a specific mode of
6 practicing the present invention, the mucopolysaccharide
7 solution includes a pharmaceutical grade viscoelastic fraction
8 which is selected preferably from hyaluronic acid or an
9 acyl-substituted hyaluronic acid or mixtures of acyl-substituted
10 hyaluronic acid and hyaluronic acid with HPMC and optionally
11 with a biocompatible surfactant; and,
12 hydroxypropylmethylcellulose (HPMC), and absent chondroitin
13 sulfate A, B, or C. The acyl-substituted hyaluronic acids have
14 alky groups with three to twenty carbon atoms. Besides the
15 viscoelastic fraction, the mucopolysaccharide solution usually
16 includes a physiological buffer fraction, conveniently in a
17 predetermined ratio to reach a suitable osmotic level. A
18 solution of between about 250 and about 400 milliosmoles is
19 generally isotonic to ocular tissues. Of course, solutions of
20 higher osmolality will potentially cause a net solute outflow
21 from ocular tissues while those of lower osmolality may permit
22 net solute migration into such tissues. When the physical
23 properties, especially surface activity, of the modified
24 mucopolysaccharide solution are closely controlled, infusion and
25 aspiration at the site of an ophthalmic operation are more
26 manageable and, particularly, the coating at the site of
27 solution contact is enhanced. In order for a solution, gel, or
28

1 the like, including mucopolysaccharide solutions of the present
2 invention, (collectively "coating agents") to coat a surface,
3 the surface tension of the coating agent must be lower than the
4 critical surface tension of the surface to be coated. Human
5 corneal endothelium is frequently found to have a critical
6 surface tension of from about 50 to about 56 dynes/cm². Thus,
7 in the practice of this invention, a coating agent having a
8 surface tension of less than about 56 dynes/cm², and more
9 particularly, less than about 50 dynes/cm² is of particular
10 advantage.

11 In addition to the above, another modified
12 mucopolysaccharide solution is disclosed. The second modified
13 mucopolysaccharide solution is used during ophthalmic surgery
14 for protection of the internal ocular structures, most typically
15 during extraction of a cataractous human lens and the
16 replacement thereof by a prosthetic intraocular lens. In
17 practicing the second embodiment of the invention, the
18 mucopolysaccharide solution includes an optically clear
19 polymeric fraction which is selected preferably from hyaluronic
20 acid; and mixtures of hyaluronic acid, and absent chondroitin
21 sulfate A, chondroitin sulfate B, and chondroitin sulfate C.

22 In the alternative, modified mucopolysaccharide solution, a
23 second fraction is that of a biologically compatible surfactant.
24 As will be described infra, many free fatty acid and similar
25 surfactants are utilizable in trace quantities to lower the
26 surface tension into the desired range. Besides the
27 viscoelastic and surfactant fractions, mucopolysaccharide
28

1 solution includes a physiological buffer fraction in a
2 predetermined ratio between the weight of the viscoelastic
3 fraction (surfactant fraction is not significant in the ratio)
4 and the weight of the buffer fraction. While the physical
5 properties of the modified mucopolysaccharide solution are
6 closely controlled, upon the modified mucopolysaccharide
7 solution being placed in the anterior chamber of the eye during
8 surgery, the surgeon can observe the ocular and intraocular
9 structure through the optically clear solution, and the corneal
10 endothelium is coated and thereby protected from accidental
11 touch by surgical instruments, ocular and intraocular prosthetic
12 devices, and in ocular and intraocular irrigating solutions.

13 Practitioners in the art frequently attempt to use
14 mucopolysaccharide solutions of particularly high viscosity.
15 However, the use of such high viscosity mucopolysaccharide
16 solutions has been limited by the difficulty encountered in
17 injecting such solutions. Frequently such solutions have not
18 been injectable at forces obtainable in hand held syringes. It
19 has now been discovered that the stress and force required to
20 inject mucopolysaccharide solutions, that is solutions
21 containing macromolecules such as HA and HPMC, decreases as
22 syringe size decreases. Thus syringe injecting a
23 mucopolysaccharide solution of given viscosity, through a needle
24 of given size, e.g. a 23 gauge needle, a 1cc syringe requires
25 substantially less force than a 3 cc syringe and a 3 cc syringe
26 less than a 5 cc syringe. (This generally presumes the standard
27 syringe configurations of inside cross section of 0.16 cm² for a
28

1 1cc syringe, 0.57 cm² for a 3cc and 1.13 cm² for a 5 cc
2 syringe.) Fig. 8 provides an exemplary table of such forces.
3 Solutions compared are A, HPMC(H); B, HA(H);, C, HA(L); D,
4 HPMC(H) and HA(L); and, E, HPMC(H) and HA(H). Clearly, the 1cc
5 syringe required less stress at maximum than the wider syringes.

6 Fig. 9(a) depicts a syringe (10) and plunger (12) with a
7 generally flat lower surface (13) particularly useful in the
8 practice of this invention. The angle θ of the flow path for a
9 viscoelastic through the syringe within the syringe into a
10 cannula (14) is seen to be about 45° or less. Fig. 9(b) depicts
11 an alternative plunger (16) for syringe (10). The lower surface
12 (18) of plunger (16) is shaped to generally conform to angle θ
13 at the bottom of syringe (10). A related embodiment is seen in
14 Fig. 9(c), wherein a syringe (20) and plunger (22) with a
15 generally bulbous lower surface (24). The flow path for a
16 viscoelastic through lower end of the syringe within the syringe
17 into a cannula (14) is seen to be about 45° or less, but sloped
18 and not linear. Unlike the usual regimen associated with
19 administration of medicaments through a syringe, the "dosage"
20 delivered here is determined by observation of the material
21 extruded from the end of the syringe. As such the amount
22 initially in a syringe or remaining in a "dead space" within the
23 syringe and not extrudable by application of pressure on the
24 plunger is of little consequence. This presumes that there is
25 sufficient extrudable capacity of viscoelastic mater to begin
26 with.

27

28

1 An embodiment of this invention is drawn to a method of
2 adhering a contact lens to the surface of the eye, and the
3 apparatus of such method. This is done to permit a medical
4 professional to clearly observe the interior of the eye. That
5 is the contact lens is typically designed for a person other
6 than the subject of the medical procedure to see into the eye.
7 To accomplish this a lens of appropriate optics and conformance
8 to corneal curvature is positioned in on the eye wherein the eye
9 surface is coated with a generally continuous sheet or layer of
10 the viscoelastic solution of this invention. In this
11 application it is particularly important that the viscoelastic
12 solution be generally transparent and bubble free. The
13 arrangement of lens on top of such viscoelastic, on top of the
14 eye permitting a view of the interior of the eye by a person
15 other than the subject is termed "operational-optical
16 connection."

17 Fig 10(a) (60) and (b) (70) are diagrammatic
18 representations of various embodiments of an apparatus for
19 viewing the interior of the eye (depicted in contact with an eye
20 (50)). Fig. 10(a) represents a side view of contact lens (64)
21 atop a layer of transparent mucopolysaccharide solution of the
22 present invention (62), positioned and optically configured so
23 that an external observer may view internal ophthalmic tissues,
24 surgical instruments, color reactions, or other observable
25 features or phenomena. Fig. 10(b), also having a layer of
26 transparent mucopolysaccharide solution of the present invention
27 (72), replaces the contact lens with the lens (74) of a camera
28 (76). In an additional embodiment, the camera could include a

1 source of illumination or laser surgical light, or be replaced
2 by or used in combination with a source of illumination or laser
3 light, such as surgical laser light, or even diagnostic light
4 application.

5 An embodiment of this invention concerns method of
6 hydraulically positioning intra-optic structures or tissues.
7 This is done by the step of applying against such tissues under
8 elevated hydrostatic pressure the modified mucopolysaccharide
9 solution of this invention. In one case, this comprises keeping
10 the lens capsule elevated and away from surgical instruments
11 during surgery such as cataract surgery. In another embodiment
12 this method would include dissecting or elevating tissue such as
13 hyperplastic tissue that has grown over the retina in certain
14 pathologies. The viscoelastic solution is introduced,
15 conveniently, through a needle at the hyperplastic tissue/retina
16 interface. Gradual injection under pressure raises up the
17 hyperplastic tissue. From this raised and free position, the
18 tissue may be removed with out substantial damage to the retina
19 tissue beneath.

20 METHODS

21 PURITY CRITERIA

22 All samples of hyaluronic acid obtained from Chesapeake
23 Biologicals passed the endotoxin Limulus Lysate Assay. The
24 criterion for passing the assay was that, when a sample was
25 dissolved with a physiological buffer to a concentration of 5
26 mg/ml, less than 0.25 endotoxin units per ml were found.

27 SURFACE TENSION

1 Surface tension was measured by a modification of the
2 Wilhelmy Plate method allowing measurement of surface tension of
3 highly viscous polymer solutions. In the Wilhelmy Plate method,
4 the surface tension was measured by immersing a thin platinum
5 blade into the solution to be measured. The blade is slowly
6 withdrawn through its attachment to a surface balance. The
7 surface balance measures the force on the platinum blade, and,
8 as the blade is pulled from the solution, a drop in force is
9 noted. The force is measured in dynes/centimeter. In the
10 modified method that was used in these experiments, surface
11 forces were measured using a sensitive transducer, (manufactured
12 by the Honeywell Co., Minneapolis, Minnesota) attached to a
13 platinum blade and recorder. For surface tensions measurements,
14 about 20 ml of solutions were placed in a petri dish. The dish
15 was placed on a jack-stand and the stand was moved upward until
16 the platinum blade just touched the solution. With this method,
17 surface forces were measured as the platinum blade was pulled
18 into the solution. In the usual Wilhelmy Plate method, the
19 surface forces are measured as the platinum blade is pulled from
20 the solution. For reproducible results, the platinum blade was
21 cleaned and exposed to a flame between usage. All measurements
22 were carried out using freshly prepared solutions at
23 temperatures of $25^{\circ} \pm 1^{\circ}\text{C}$.

24 In some instances, surface tension was measured at 25°C
25 using a tensiometer (Cahn, Model DCA 322, Cerritos CA). Twenty
26 ml of a solution being tested was poured out into a Pyrex™ cover
27 dish and placed on the stage of a tensiometer. All tests were
28 performed at about $17\text{-}25^{\circ}\text{C}$ ("room temperature") using a platform

1 speed of 104 microns/sec. Data was collected using an IBM-PC™
2 and DCA-322™ software to obtain surface tension of the receding
3 curve for the material tested.

4 PREPARATION OF VISCOELASTIC SOLUTIONS

5 All polymer solutions were diluted to the desired
6 concentration. A buffer solution containing 0.85% sodium
7 chloride, 0.028% disodium hydrogen phosphate dihydrate and
8 0.004% of sodium hydrogen phosphate hydrate. The dilution
9 varied according to the desired viscosity.
10

11 EXAMPLE 1

12 Sodium hyaluronate + oleic acid

13 Hyaluronate with an average molecular weight of under
14 50,000 (Chesapeake Biologicals) was dissolved in buffer solution
15 at room temperature. Potassium oleate was added to achieve a
16 final concentration of 5×10^{-6} mg./ml.

17 EXAMPLE 2

18 Acyl-substituted hyaluronate

19 Acyl-substituted hyaluronate was diluted utilizing
20 phosphate buffer to a final concentration of 30 mg./ml.

21 EXAMPLE 3

22 Acyl-substituted hyaluronate + oleic acid + hyaluronate)

23 Acyl-substituted hyaluronate and hyaluronate together
24 having an average molecular weight of 1×10^6 , were diluted in
25 phosphate buffer to achieve a final concentration of 30 mg./ml
26 of sodium hyaluronate and 1 milligram per ml of acyl-substituted
27 hyaluronate. Oleic acid was added to the final solution to
28 achieve a concentration of 1×10^{-6} mg./ml. of potassium oleate.

Example 4

Preparation of acyl-substituted hyaluronic acid

Bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is utilized to prepare the substituted hyaluronate. Hyaluronate is dissolved in a dilute sulfuric acid solution and titrated with sulfuric acid to a final pH of 3.0. The solution is heated to 75° C and the acyl anhydride, for example N-butyric, is added to the solution. The solution is constantly stirred. The molar ratio of the two solutes is adjusted to achieve substitution of one hydroxyl group by an acyl group at every 4th to 10th repeating disaccharide unit of hyaluronic acid. The reaction is then allowed to run to completion over an extended period, approximately 24 hours. The solution is then neutralized with 0.1N sodium hydroxide and subsequently dehydrated. The resultant dried solute is used to form subsequent solutions.

Utilizing sodium hyaluronate with molecular weights in the range of 500,000 to 2×10^6 , an acyl-substituted hyaluronate, and a biologically compatible surfactant, viscoelastic formulations can be made with any desired surface tension, which is compatible with ocular and intraocular use, and which fracture with suction forces in the range of 5 to 400 mm Hg. depending upon the solution properties desired. Unique formulations can be constructed which affect coating of ocular and intraocular structures yet which can be completely aspirated or retarded from aspiration as so desired.

Example 5 Blending Technology

1 In order to achieve a solution with appropriate fracturing
2 characteristics, two hyaluronic acid species of different
3 average molecular weights were utilized. Both hyaluronic acid
4 fractions were obtained from rooster combs from Chesapeake
5 Biologicals. One fraction had an average molecular weight of 1×10^6
6 Daltons and supplied in a 5 mg/ml concentration. The
7 other fraction consisted of an acid species with an average
8 molecular weight of 500,000 in a concentration of 30 mg/ml. From
9 these two species, solutions were constructed based on a volume
10 ratio of one part low molecular weight to two part high
11 molecular weights, hyaluronic acid. At this ratio of molecular
12 weights, the viscous mixture easily fractured when suctioned
13 through a 0.3 mm aspiration cannula when vacuum pressures were
14 applied in the range of 50 to 200 mm Hg. Verification of
15 fracturing characteristics was achieved by direct visualization
16 through a 10X microscope.

17 Quantification

18 Viscoelastic solutions meeting the claimed characteristics
19 are directly determinable. Typically a solution of about 4% to
20 about 10% viscoelastic selected from, for example, the group
21 consisting of acyl-substituted hyaluronic acid having acyl
22 groups thereof with three to twenty carbon atoms, hyaluronic
23 acid, hydroxypropylmethylcellulose and mixtures thereof is
24 useful. Clearly, higher initial percentage concentrations can
25 be employed. Serial dilutions, conveniently in 10x steps are
26 then made, and the viscosity and surface tension repeatedly
27 measured until the desired point is reached. In addition,
28 biocompatible surface active agents may be employed to reduce

1 surface tension. In mixtures of HPMC and hyaluronic acid, and
2 derivatives thereof, it is useful to note that HPMC contributes
3 little to viscosity while possessing surface activity, while
4 hyaluronic acid and derivatives thereof contribute substantially
5 to viscosity and little to surface activity. In practice a
6 checkerboard dilution and proportion type assay provides a
7 convenient system for determining component proportions within
8 the claimed range. The accompanying graphs, particularly Figs.
9 6 and 7 will assist in the interpretation of checkerboard
10 results by directing one to the proper parameter by modification
11 of the proper constituent.

12 **Viscosity Measurements**

13 Tested solutions were removed from storage at 4°C and
14 allowed to reach room temperature. After reaching room
15 temperature, 5ml of such solution was injected onto the sample
16 testing plate of a viscometer, Rheometrics Fluids Spectrometer
17 #RFS8400™ (Piscataway, N.J.). The shear rate was linearly
18 increased from 0.3 sec⁻¹ to 9.0 sec⁻¹ over a period of 9
19 minutes,
20 and the viscosity of the solution recorded with a Haake RV 100
21 plotter. From a plot of viscosity v. shear rate, the viscosity
22 at 0.35 sec⁻¹ was extrapolated.

23 **Molecular Weight**

24 Molecular weight may be determined by any of a number of
25 well known techniques such as chromatography and density
26 centrifugation. A particularly useful method of measuring
27 molecular weight was by the scattered light intensity at an
28 angle of 6-7° using a Chromatic KMX-6™ laser light scattering

1 device. A detailed description of this method is set forth in
2 "Laser Light Scattering measurements on Vitreous and Rooster
3 Comb Hyaluronic Acids," Int.J.Biol.Macromol., 4:425-9 (1982)
4 incorporated herein by reference. The Optical constant required
5 for molecular weight determinations was obtained using a
6 chromatix KMC-16™ differential refractometer operating at 5°C
7 and at a wavelength of 633nm. The instrument was calibrated by
8 measuring the difference in the refractive index of standard
9 salt solutions with water as the reference material. Once the
10 calibration constant was determined from measurements on salt
11 solutions, the difference in refractive index between each
12 solution and its dialysate was measured at concentrations
13 between 1 and 5mg/ml. The ratio of change in refractive index,
14 Δn , divided by the concentration, c , was plotted against
15 concentration and the value of the refractive index was taken as
16 $\Delta n/c$ extrapolated to zero concentration.

17 Molecular weight was then obtained by determining the
18 Rayleigh factor, (R_θ) for solutions of unknown concentration, c ,
19 between 0.1 and 0.5 mg/ml and plotting Kc/R_θ against
20 concentration (K , the optical constant is calculated using
21 refractive index increment) as shown in Fig. 1, with a
22 calculated molecular weight of 5,560,000. Weight average
23 molecular weight was determined from the reciprocal of Kc/R_θ
24 extrapolated to zero concentration.

25 Injection Tests

26 A particular injection load versus time curve is set forth
27 in Fig. 2. The material tested was a high molecular weight HA.
28 Maximum load was determined as the largest load needed to force

1 the sample from a syringe through a 23 gauge needle. While
2 testing may be accomplished various ways known in the art, HA
3 and HPMC solutions were conveniently tested using a syringe
4 holder fashioned to attach to the compression cell of an Instron
5 Tester Model 1122 (Instron Corp, Springfield, N.J.). Force was
6 measured from the load cell and the crosshead was lowered at a
7 rate of 200mm/min. Maximum stress was determined by dividing
8 the peak load by the cross sectional area (interior) of the
9 syringe barrel.

10 **Aspiration Profile**

11 Aspiration behavior was uniformly determined by use of a 23
12 gauge needle. Test procedure entailed placing a vacuum through
13 the 23 gauge needle onto each sample and determining the
14 fraction of each sample aspirated within 1 minute. The vacuum
15 was increased in 22 mm Hg increments from 0 to 100 mm Hg and the
16 fraction aspirated was determined gravimetrically. From the
17 data represented in Fig. 5, the distinct aspiration
18 characteristic of the viscoelastic solutions of this invention
19 are made clear. The inventive solutions do not aspirate as a
20 bolus at any applicable vacuum level. Of particular importance
21 is the substantially non-sigmoidal curve found upon aspiration
22 of solutions of this invention under the conditions used in
23 compiling the data of Fig. 5. In contrast, HA solutions of
24 comparable viscosity, aspirate as bolus at all but the lowest
25 vacuum levels. In practice, at aspiration vacuum levels
26 designed to provide reasonably prompt removal of less than the
27 total amount of viscoelastic solution, only the inventive
28 solutions will suffice. The shaded area of Fig. 5(a) generally

1 delimits the particular aspiration characteristic of less than
2 total aspiration of viscoelastic solution of the present
3 invention at vacuum levels above about 50 mm Hg. The aspiration
4 curves at the vacuum levels tested offers reasonable
5 predictability as to those aspiration characteristics that will
6 permit a medical professional to incrementally aspirate a
7 viscoelastic at convenient pressures and over a fairly brief
8 period of time. Solutions with sigmoidal curves aspirate
9 essentially as a bolus and are not suitable. In the 50 to 90
10 mmHg range under this procedure, and limited to solutions that
11 are substantially non-sigmoidal in aspiration behavior, a slope
12 of from about horizontal up to about 1.5 and more particularly
13 from about horizontal to about 1.0 are preferred, with a slope
14 or aspiration profile of about horizontal to about 0.5 more
15 preferred. It is understood that the slope of an horizontal line
16 is technically an undetermined special case. However, a
17 slightly upward line has a slope of a small positive number.
18 For convenience here, the slope of an horizontal line will be
19 assumed to be zero, and the stated range from horizontal up to
20 slopes of 1 and 1.5, includes horizontal (or even slightly
21 negative slopes). While very high or low vacuum levels or
22 aspiration times are conceivable, they are less useful, except
23 in unique circumstances. Unduly high aspiration vacuum levels
24 pose a danger to ocular structures. Unduly long aspiration
25 times, generally in excess of 2 or 3 minutes, unduly prolong
26 surgical procedures.

27

28

1 Again referencing Fig. 7, Aspiration profile is presented
2 in Z axis, forming, as plotted against viscosity and surface
3 tension a theoretical cube of the claimed viscoelastic solution.
4 Points A, B, C and D are at a viscosity of 100,000 mPa.s.
5 Points E, F, G, and H are at a viscosity of 10,000 mPa.s.
6 Points A, D, E, and H are at Aspiration Profile of 0. Points B,
7 C, F, and G are at Aspiration Profile points of 1.5. Points A,
8 B, E, and F are at Surface Tension of 40 dynes/cm. Points D, C,
9 H and G are at Surface Tension of 65 dynes/cm. Point I
10 represents Occucoat and point II represents Healon, each beyond
11 the enclosed area.

12 With the techniques and examples described above, the novel
13 and unobvious modified mucopolysaccharide solutions of this
14 invention are presented in the claims which follow. Minor
15 changes and adjustments may be made by those skilled in the art
16 without departing from the spirit of this invention.
17
18
19
20
21
22
23
24
25
26
27
28

TABLE 1. *Products and solutions used or tested for use in ophthalmic surgery*

Product	Manufacturer	Polymer	Concentration	Molecular weight
Healon	Pharmacia	HA	10	~4,000,000
Amvisc	Med-Chem Products	HA	~10	~2,500,000
IaL	Fidia	HA	20	~500,000
Viscoat	Cilco	HA +	30	~500,000
		CS	40	~30,000
CS 50%	—	CS	500	~20,000
HPMC 2%	—	HPMC	20	~100,000
Collagen	3M	Collagen	20	320,000 → gel

HA—hyaluronan, CS—Chondroitin sulphate,
 HPMC—hydroxypropylmethylcellulose.

1
2
3 **WHAT IS CLAIMED;**

4 Claim 1. The modified mucopolysaccharide solution for use
5 as a biologically active therapeutic infusion comprising:

6 a pharmaceutical grade viscoelastic fraction selected from
7 the group consisting of acyl-substituted hyaluronic acid having
8 acyl groups thereof with three to twenty carbon atoms,
9 hyaluronic acid, hydroxypropylmethylcellulose and mixtures
10 thereof, and absent chondroitin sulfate said fraction having a
11 surface tension of between 40 and 65 dynes/cm²; and,

12 said modified mucopolysaccharide solution having a
13 viscosity of between 10,000 and 100,000 centipoise when measured
14 at a shear rate of 3 sec⁻¹ at 25°C.

15 Claim 2. A modified mucopolysaccharide solution as
16 described in Claim 1 having a surface tension of less than about
17 56 dynes/cm².

18 Claim 3. A modified mucopolysaccharide solution as
19 described in Claim 2 having a surface tension of less than about
20 50 dynes/cm².

21 Claim 4. A modified mucopolysaccharide solution as
22 described in Claim 1 wherein said viscoelastic fraction has an
23 average molecular weight of at least 50,000.

24 Claim 5. A modified mucopolysaccharide solution as
25 described in Claim 1 wherein said viscoelastic fraction is an
26 acyl-substitute hyaluronic acid having acyl groups thereof with
27 three to twenty carbon atoms.
28

Claim 6. A modified mucopolysaccharide solution as described in Claim 1 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.

Claim 7. A modified mucopolysaccharide solution as described in Claim 6 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 8. The modified mucopolysaccharide of Claim 7 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 9. A modified mucopolysaccharide solution as described in Claim 4 wherein said viscoelastic fraction is a mixture of said acyl-substituted hyaluronic acid and hyaluronic acid.

Claim 10. A modified mucopolysaccharide solution as described in Claim 9 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.

Claim 11. A modified mucopolysaccharide solution as described in Claim 10 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 12. The modified mucopolysaccharide solution of Claim 1 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 13. The solution of Claim 12 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 14. A modified mucopolysaccharide solution as described in Claim 12 further including the surfactant is oleic acid.

Claim 15. The modified mucopolysaccharide of Claim 12 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 16. A modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with

three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm²; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec⁻¹ at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 17. A modified mucopolysaccharide solution as described in Claim 16 having a surface tension of less than about 56 dynes/cm².

Claim 18. A modified mucopolysaccharide solution as described in Claim 17 having a surface tension of less than about 50 dynes/cm².

Claim 19. A modified mucopolysaccharide solution as described in Claim 16 wherein said polymeric fraction is hyaluronic acid.

Claim 20. The modified mucopolysaccharide solution of Claim 16 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 21. The solution of Claim 20 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 22. A pharmaceutically acceptable modified mucopolysaccharide solution absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm²; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec⁻¹ at 25 C.

Claim 23. A modified mucopolysaccharide solution as described in Claim 22 having a surface tension of less than about 56 dynes/cm².

Claim 24. A modified mucopolysaccharide solution as described in Claim 23 having a surface tension of less than about 50 dynes/cm².

Claim 25. The solution of claim 22 wherein said mucopolysaccharide is a surface active mucopolysaccharide.

Claim 26. The solution of claim 25 further comprising a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Claim 27. The solution of Claim 22 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 28. The solution of Claim 27 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 29. The solution of Claim 22 wherein said mucopolysaccharide has an average molecular weight of at least 50,000.

Claim 30. The solution of Claim 29 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 31. The solution of Claim 30 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 32. A method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the step of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm²; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec⁻¹ at 25 C.

Claim 33. The method of Claim 32 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 cm² in cross section or less.

Claim 34. The method of Claim 32 wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm².

Claim 35. The method of claim 34 wherein the modified mucopolysaccharide solution has a surface tension of less than about 50 dynes/cm².

Claim 36. The method of claim 32 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 37. The method of claim 36 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 38. A method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm²; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec⁻¹ at 25 C.

Claim 39. The method of Claim 38 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 40. A modified mucopolysaccharide solution as described in Claim 38 having a surface tension of less than about 56 dynes/cm².

Claim 41. A modified mucopolysaccharide solution as described in Claim 40 having a surface tension of less than about 50 dynes/cm².

Claim 42. The method of claim 41 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 43. The method of claim 42 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 44. A method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm²; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 45. The method of Claim 44 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 46. The method of claim 44 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 47. The method of claim 46 wherein said solution, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 48. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm²; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C .

Claim 49. A modified mucopolysaccharide solution as described in Claim 48 having a surface tension of less than about 56 dynes/cm^2 .

Claim 50. A modified mucopolysaccharide solution as described in Claim 47 having a surface tension of less than about 50 dynes/cm^2 .

Claim 51. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion as delimited by the shaded area of Fig. 7.

Claim 52. A method of adhering a contact lens to the surface of the eye in operational-optical connection with said eye, by the step of interposing between said lens and said eye surface an adhering amount of substantially transparent modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm^2 ; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec^{-1} at 25°C .

Claim 53. A method of hydraulically positioning intra-optic structures or tissues by the step of applying against such tissues under elevated hydrostatic pressure modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm²; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec⁻¹ at 25°C.

Claim 54. The method of Claim 53 wherein the tissue is hyperplastic tissue, positioned over the retina and said applying is performed by injecting said solution between said tissue and the retina, said positioning resulting in raising the tissue off of the retina.

FIG. 1

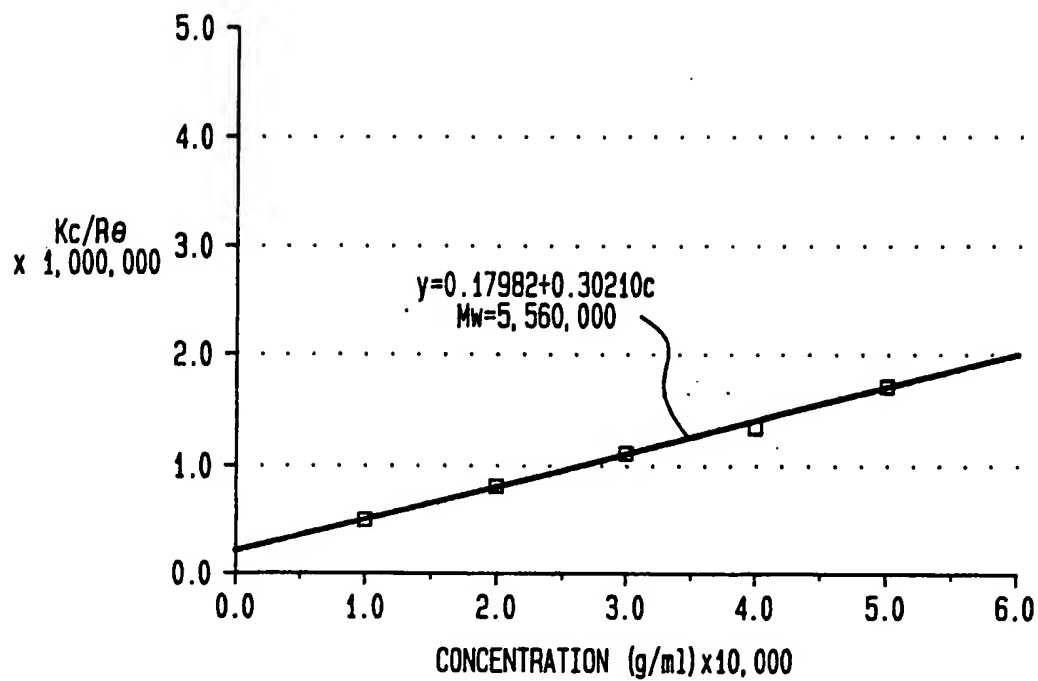


FIG. 2

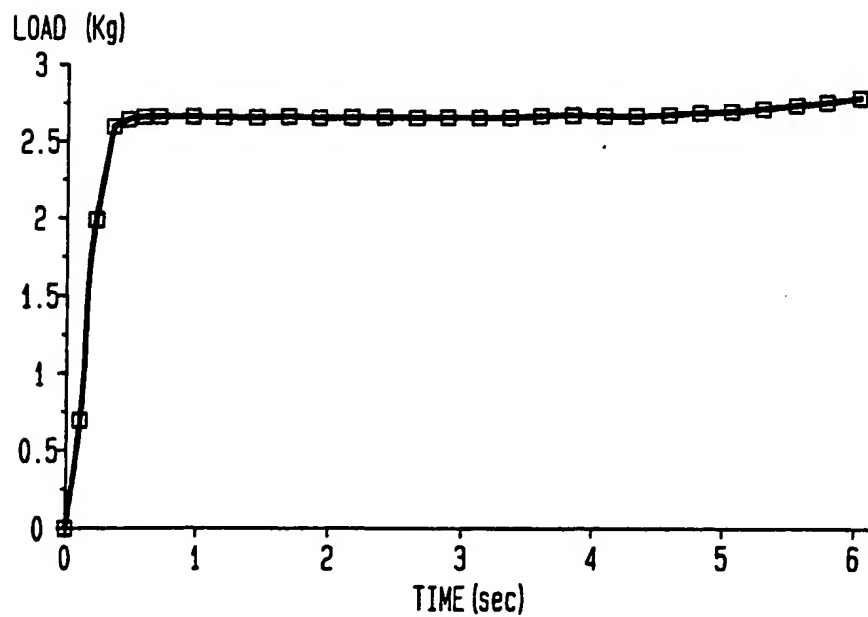


FIG. 3

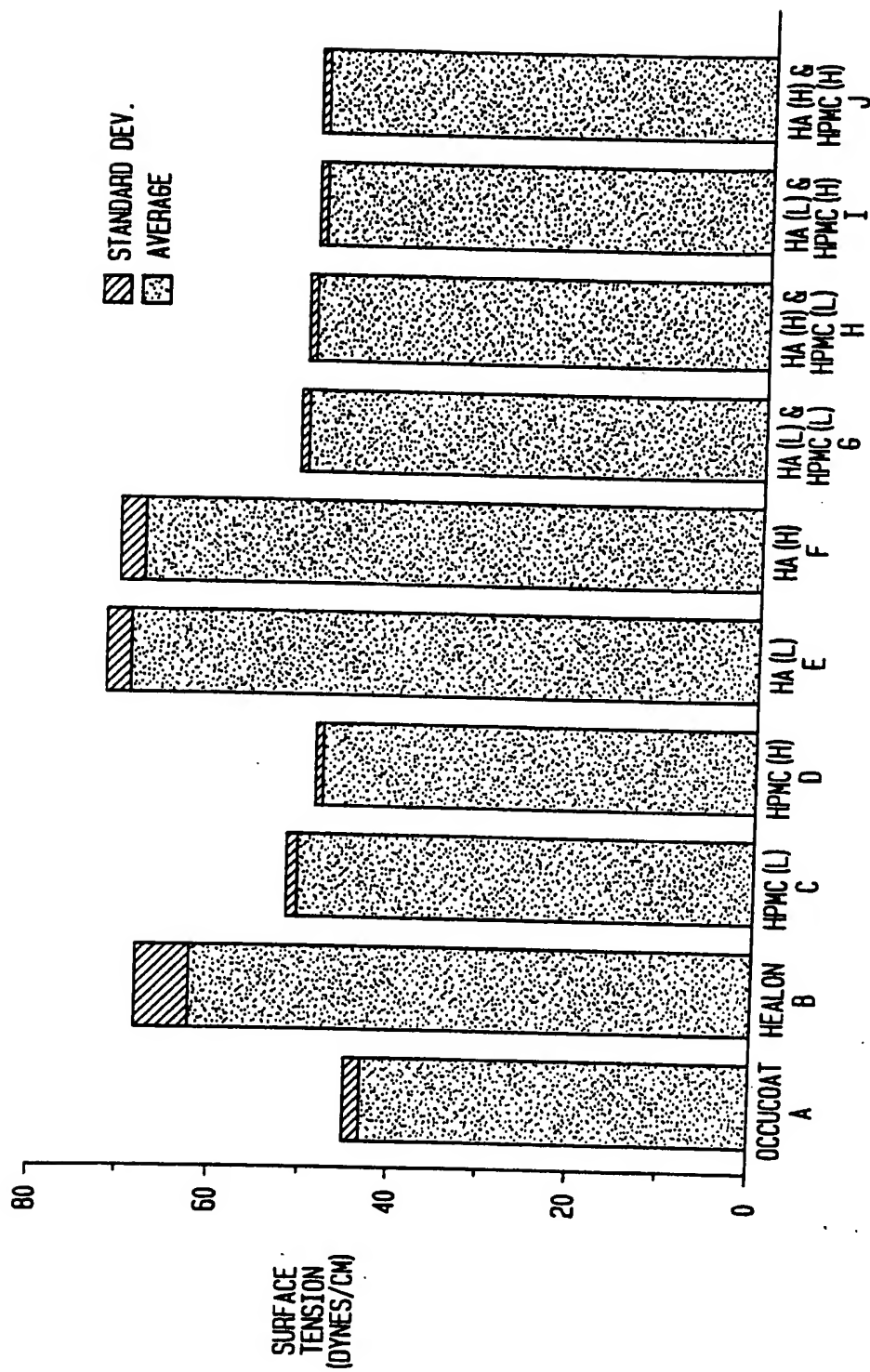


FIG. 4

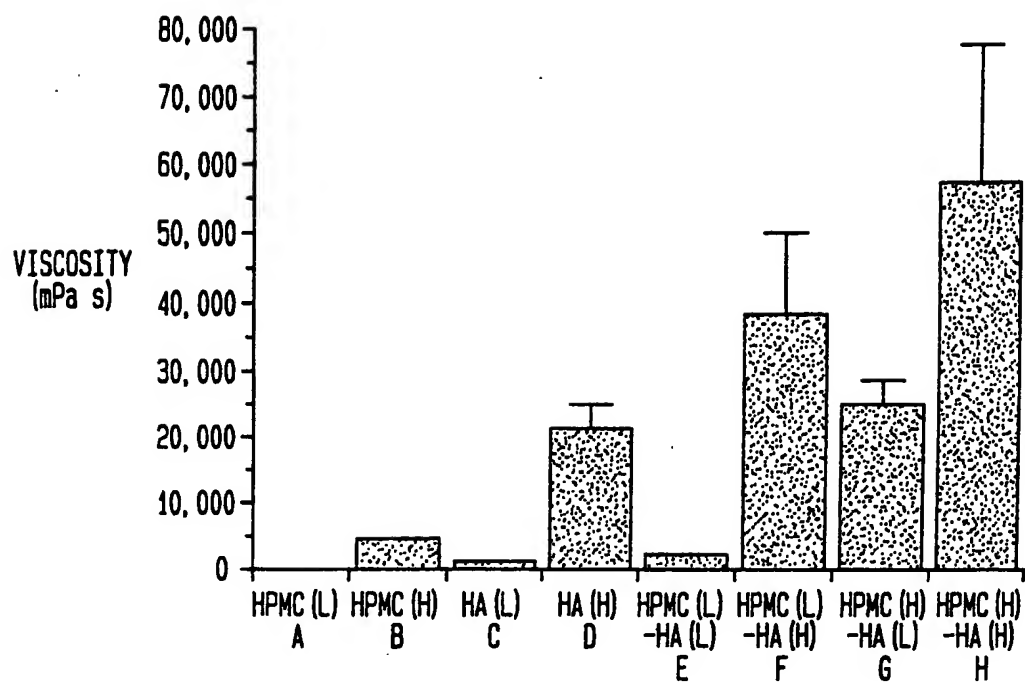


FIG. 5

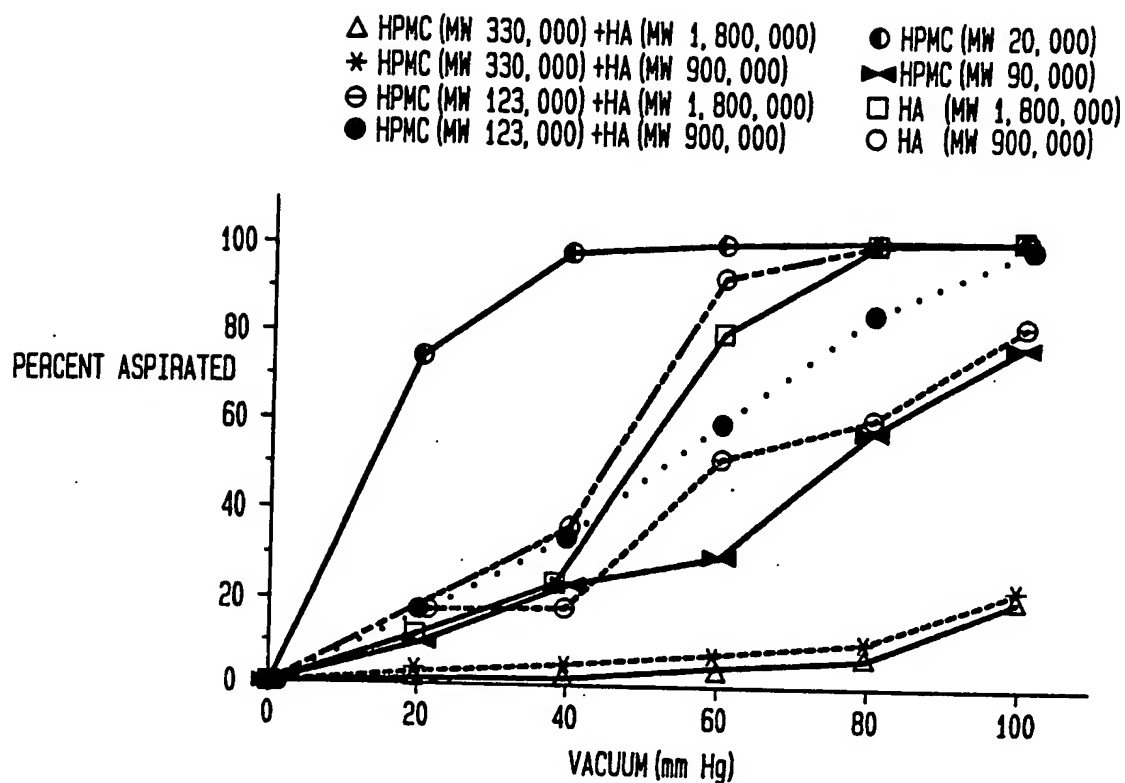


FIG. 5A

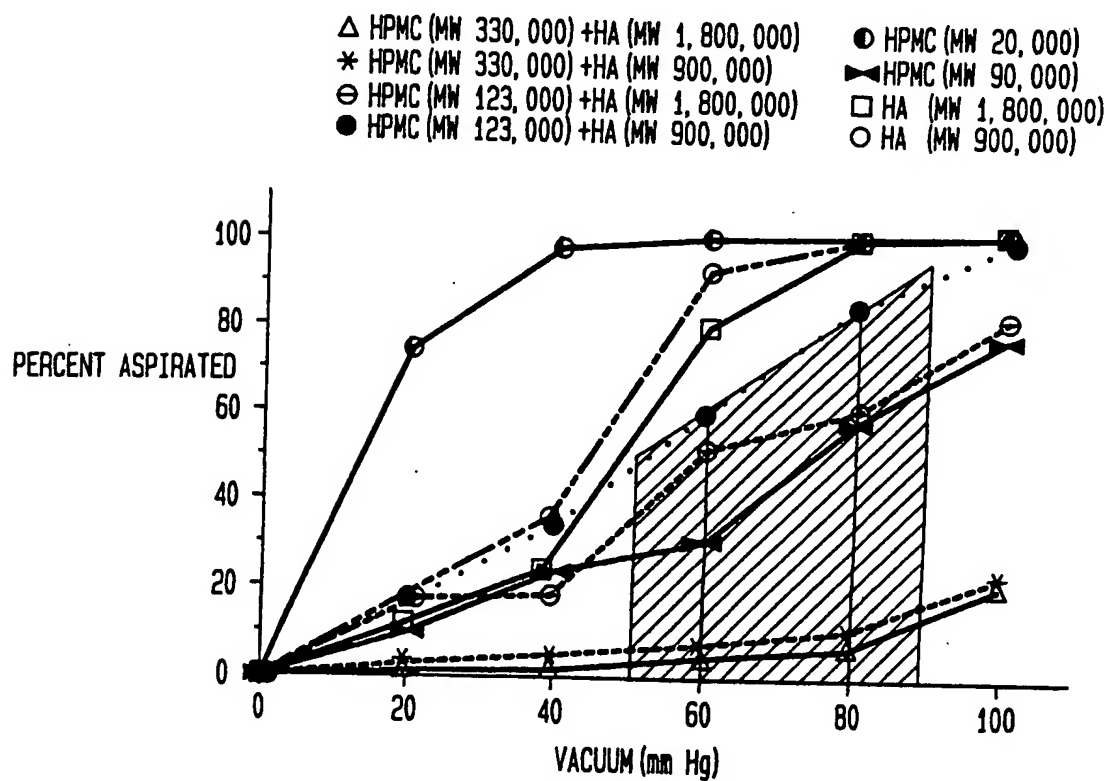


FIG. 6

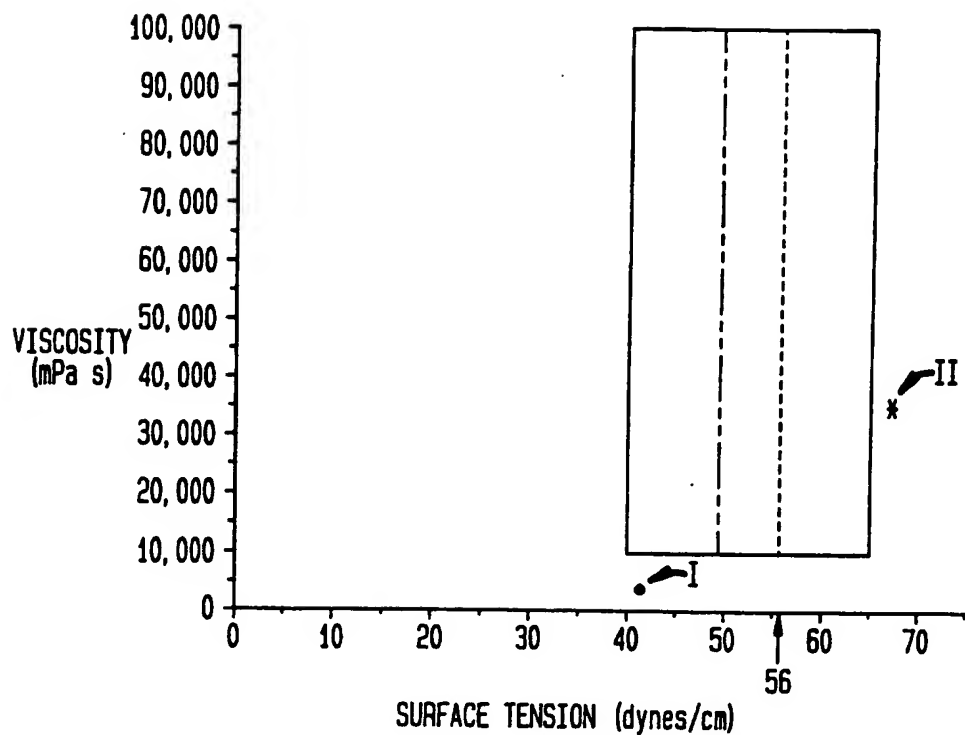


FIG. 7

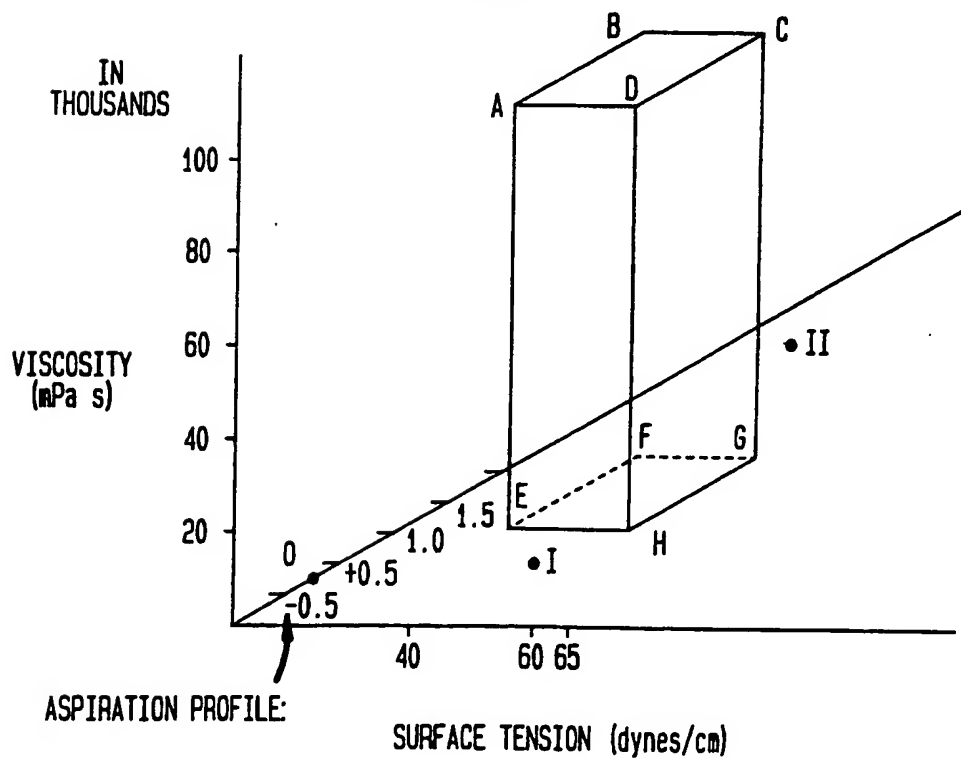


FIG. 8

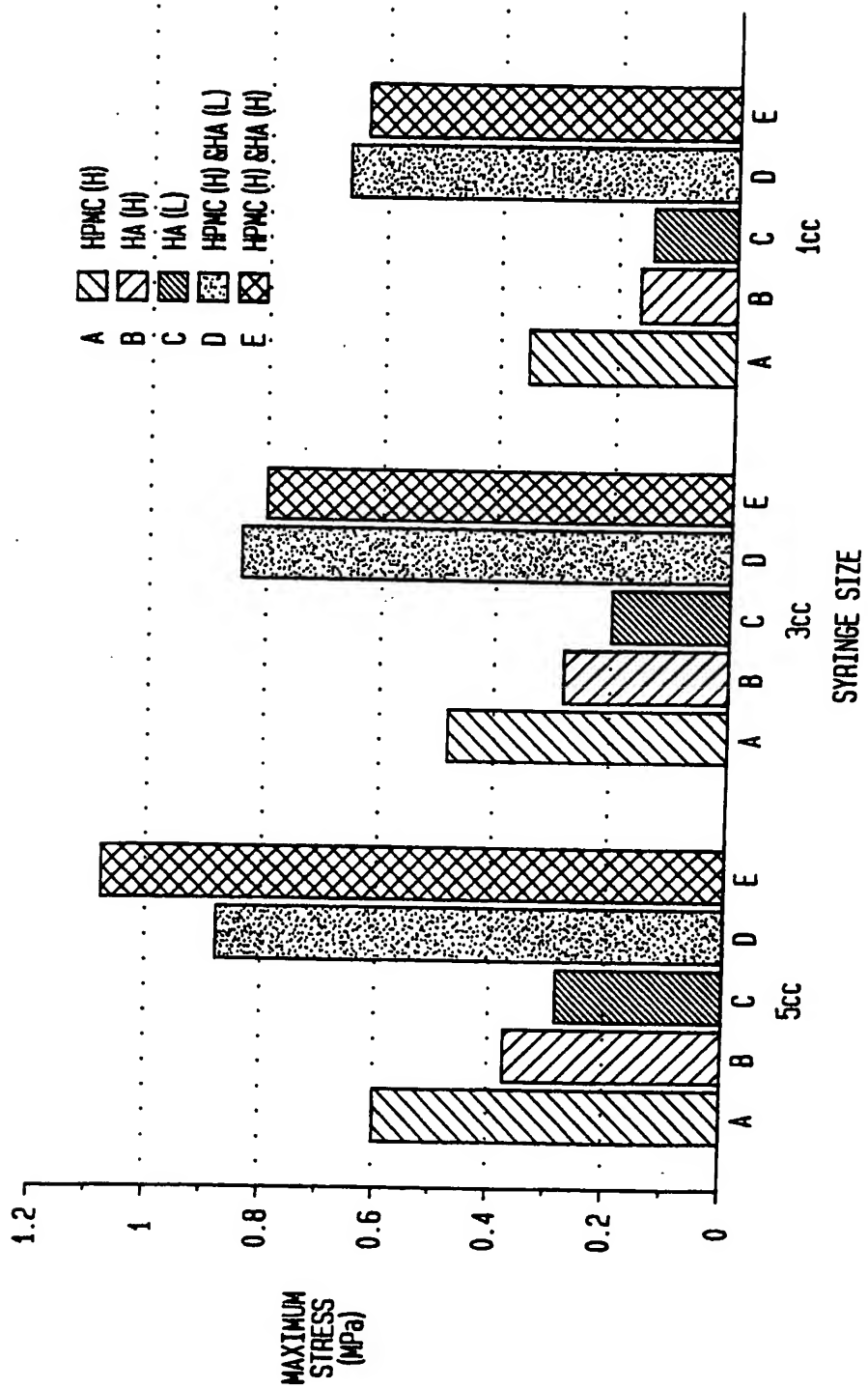


FIG. 9A

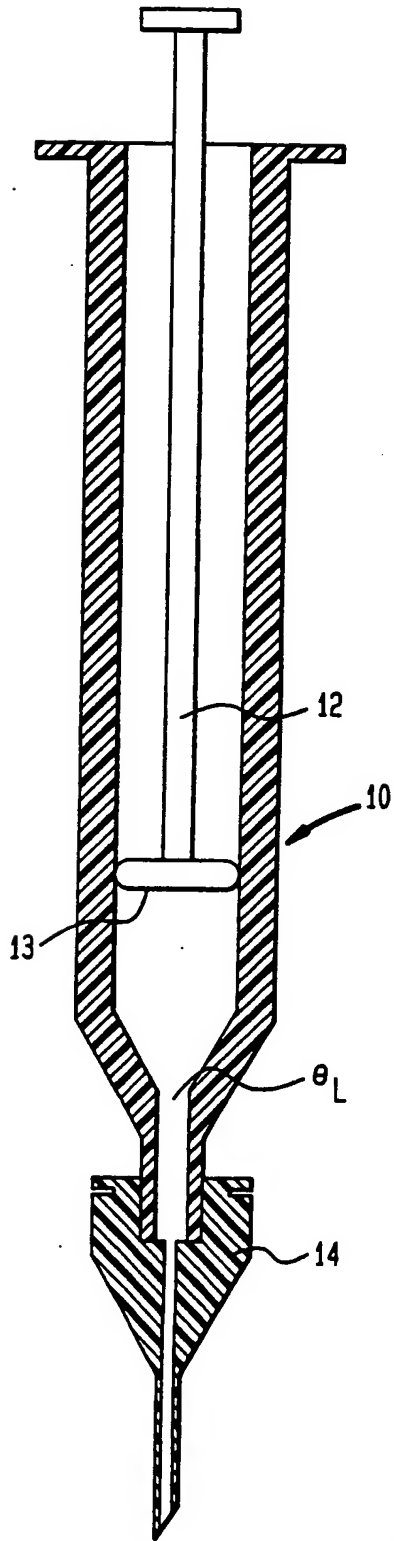


FIG. 9B

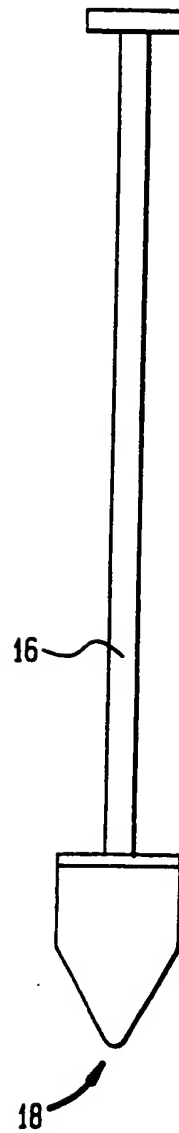


FIG. 9C

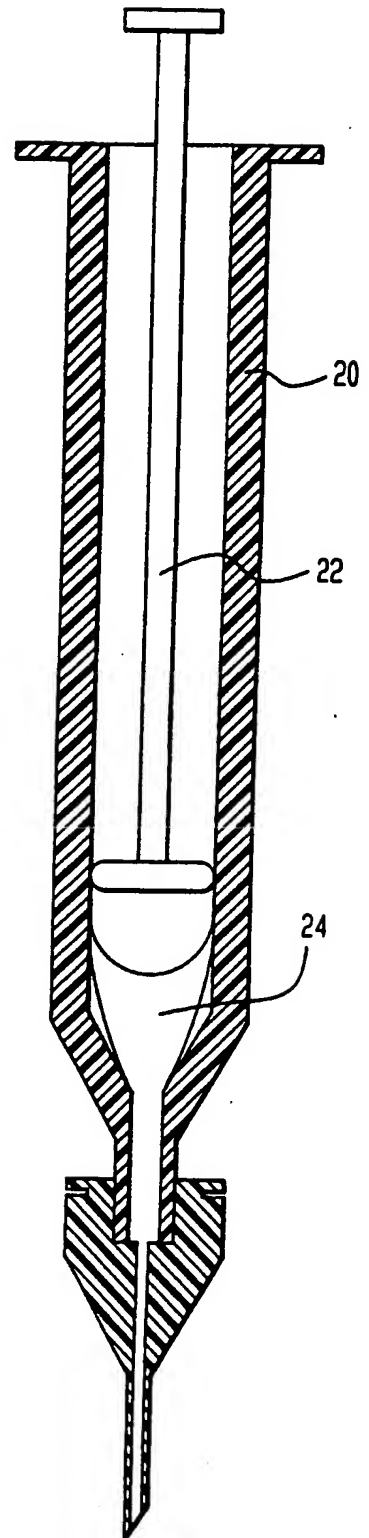


FIG. 10A

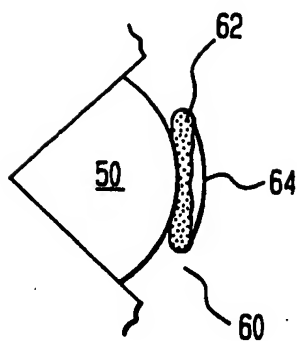
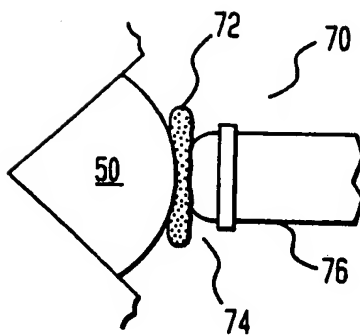


FIG. 10B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10175

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/70; A61F 13/20; G02C 7/02

US CL : 514/54; 351/177; 604/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54; 351/177; 604/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,713,375 (LINDSTROM ET AL.) 15 December 1987, col. 1, lines 22-37 and col. 2, lines 1-3.	1-51
Y	US, A, 4,767,463 (BRODE ET AL.) 30 August 1988, col. 12, lines 17-42.	6-8, 10-11, 26
Y	US, A 4,851,521 (DELLA VALLE ET AL.) 25 July 1989, col. 1, lines 48-68, col. 3, lines 3-59.	1-51
Y	Survey of Ophthalmology, Volume 34, No. 4, issued January-February 1990, Liesegang et al, "Viscoelastic Substances in Ophthalmology", pages 268-293, especially pages 269-272.	1-51

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A	document member of the same patent family
*O document referring to an oral disclosure, use, exhibition or other means		
*P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

02 DECEMBER 1994

Date of mailing of the international search report

DEC 28 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ELLI PESELEV

Telephone No. (703) 308-0196